REMARKS

After entry of this paper, the pending claims are 74, 76, 79, 81-84, 87, 90 –101, 103-110, and 113-186. Claims 1-73, 75, 77-78, 80, 85-86, 89, 102 and 111-112 are canceled without prejudice to refiling in a properly filed continuation.

Claim and Specification Amendments and New Claims

A copy of all amended and new claims are presented in logical order (without underlining and strikeout) for ease of review as Appendix A attached to this response.

Claims 74, 76, 79, 81-84, 87, 88, 90 –101, 103-109, 113-116, 118-139 are amended to correct dependencies from the new independent claims, remove redundant language, and to otherwise clarify the invention in claim language. Support for these amendments are found throughout the specification, and specifically at pages 5, lines 1-8, 26-27; page 6, lines 8-12; page 10, line 17-page 11, line 12; page 13, lines 11-17, page 23, lines 26-30, page 26, lines 6-10 and SEQ ID NO: 18.

New claims 140-186 are supported by original claims 1, previously presented claims 73, 85, 89, 111, 112 and throughout the original specification, as indicated below. Specifically, new independent claims 140 and 160 are supported by original claim 1, and specification page 6, lines 5-9, 14-26, and 28-29; page 8, lines 29-30; page 9, lines 1-4, 15-17, and 21-25 and page 10, lines 21-22. Claims 141, 165 and 174 are supported at page 6, lines 26-27. Claims 142, 166 and 175 are supported at page 6, line 27; page 7, lines 5-6; page 9, lines 12-13, page 24, lines 2-8 and 18; page 25, lines 5-8, 12 and 19; page 27, line 19; page 28, lines 6-8, 14, 16-19. Claim 143 is supported at pages 6 , line 23 and by SEQ ID NO: 18. Claim 144 is supported at page 7, line 11. Claims 145, 169 and 170 are supported at page 7, lines 5-6. Claims 146, 147, 171 and 172 are supported by the support for Claim 140 and also at page 6, line 20, and by the example of 1-aminocyclohexanecarboxylic acid in the specification. Claims 148-149 are supported at page 8, lines 15-28 and by SEQ ID NO: 18. Claim 150 is supported at page 7, line 11. Claims 151 and 152 are supported at page 9, line 2. Claims 152-153 are supported at page 9, lines 12-13; page 24, line 28; page 25, lines 5-19; page 27, line 19; page 28, lines

6-8, 14 and 16-19. Claims 155, 176 and 177 are supported at page 8, line 30 to page 9, line 1; page 9, line 9; page 25, lines 5-8; page 27, line 19; page 28, lines 6-8, 14 and 16-19 and SEQ ID NO: 18. Claims 156-159 and 161-164 are supported at page 9, lines 21-25. Claim 166 is supported at page 6, lines 28-29. Claim 168 is supported at page 6, line 20. Claim 173 is supported at page 8, lines 30 to page 9, line 4. Claim 178 is supported by original claim 18 and page 26, line 12. Claim 179 is supported by original claim 39, and page 54, lines 6-7. Claim 180 is supported by original claim 40, and page 3, lines 26-28. Claims 181-183 are supported by page 11, lines 11-22. Claim 184 is supported by page 10, line 26 and page 11, lines 15-16. Claim 185 is supported at page 11, line 19. Claim 186 is supported at page 11.

The amendments to the specification pages were made to clarify that the R^2 structure depicted throughout the specification in certain of the peptides was the amide of β-acetyl-2,3-diaminopropionic acid. This amendment is clearly supported by the depicted structures and description of the exemplified peptides.

No new matter is added by these amendments

Specification Objections

The examiner objected to the presentation of the claim peptide formula on page 3, lines 5-7 and suggests the formula be presented as R^1 -SEQ ID NO: 1-R^2 to conform with the sequence listing.

Applicants respectfully request reconsideration and withdrawal of this objection in view of the above-noted amendment to the specification at page 3, incorporating the examiner's suggestion.

35 USC § 112, First Paragraph, Rejection

The Examiner has rejected claims 1, 73-76, 79 and 81-132 under 35 USC § 112, first paragraph because the specification allegedly does not reasonable provide enablement for the formula R^1 *-SEQ ID NO:1-* R^2*, requiring correction of claim 1 and 85.*

Further the claims do not set forth whether cleavage is enzymatic or by acid, or what specific enzyme is referenced. The specification does not define "unnatural amino acids", or how such unnatural amino acids will affect the peptide and its function. The examiner requires that the specification set forth what residues will be added or inserted into the claimed sequence based on a structure/function relationship. The specification is required to set forth specific examples of the claimed modifications.

The examiner further rejects the broad definition of R^1 *as having a net positive charge. The examiner requires* R^1 *to be defined.*

The examiner further alleges that the specification does not specifically identify Thr as being de-glycosylated.

The dependent claims are rejected for not disclosing the structure or any indication of where additional peptides will attach within the sequence. Because claim 1 lacks an indication of function, the examiner questions whether modified peptides will retain the function. The language such as "addition of up to 15 amino acids", "greater than 3 amino acids", the spacer duplicates at least a portion of the peptide: do not set forth the structure of the claimed peptide in Claims 1, 73, 85, 108, 114 or 118.

Applicants respectfully request reconsideration and withdrawal of this rejection for the following reasons.

Claim 1 has been canceled without prejudice to refiling in a properly filed continuation application. New claim 140 is presented and incorporates the correction to the sequence as R^1 -SEQ ID NO: 1- R^2, as requested by the examiner. Claim 140 defines with specificity sites X-Y and X'-Y', which description is supported by the specification at page 9, lines 21-29 and page 22, lines 24-30. Thus the new claim eliminates the need for the rejected "cleavage" language.

Applicant respectfully traverses the examiner's assertion that the term "unnatural amino acid" requires description. An unnatural amino acid is a term of skill in the art describing any amino acid residues that are **not** naturally occurring. Because there are only 20 naturally occurring amino acids[1], any modification in the chemical structure of the amino acid, such as by substitution of another chemical group, like an alkyl, a sugar, etc., creates an unnatural amino acid. In the specification, examples of such "unnatural"

[1] "Proteins are built from a repertoire of twenty amino acids" Lubert Stryer, Biochemistry, 3rd edit, Freeman and Co., NY, NY, pp. 16-21.

amino acids are provided as D configuration amino acids (pg. 6, line 27), amino acids that improve stability in serum (pg. 22, lines 29-30), the residues 1-aminocyclohexane carboxylic acid (Chex)[2] or 2-3-diaminoproprionic acid (Dap) (pg. 31, line 22). Still other unnatural amino acids are conventional in the art. See, the cited references relating to N-methylated amino acids, among others.[3]

Further the nature of R^1 has been defined by incorporating the description provided in claim 89 and clearly exemplified throughout the specification and in the examples. The specification itself presents 17 examples of modified peptides falling under the scope of claim 140. According to these examples R^1 is exemplified as:

examples of claim 140(d) - Val and D-Val;

examples of 140 (d) - Acetyl-Lys-Val-Asp-Lys-Val, Acetyl-Arg-Val, and Acetyl-Lys-Val;

example of 140(d) - Arg-Pro-Pro-Thr-Pro-Arg-Pro-Leu-Lys-Val;

examples of 140(c) or (d) - Biotin-Lys-Val and 5(6)-carboxyfluorescein-Lys-Val; and

example of a cyclic alkyl of 140 (a)/(b) - a 1-amino cyclohexane carboxylic acid group.

In addition, Applicant's subsequent publications M. Cudic *et al*, **2002** Peptides 23:2071-2083 and A. Bencivengo et al, **2002** Lett. Pept. Sci., 8:201-209 and M. Bower et al, **in press 2004** Lett. Pept. Sci., 00:1-11, provide additional examples falling within the scope of R^1, including 4-amino-4-carboxy-piperidine (an example of a cyclic alkyl of 140(a) and a sequence of 12 additional amino acids (Thr-Tyr-Gln-Arg-Thr-Arg-Ala-Leu-Val-Lys-Lys-Val (an example of 140 (d)), among others.

Applicants respectfully submit that these numerous examples of R^1 groups falling within the definition now incorporated into claim 140 should satisfy the section 112, first paragraph requirements for this claim.

---

[2] Note that Chex can also properly be categorized as a cyclic alkyl when used as an R1 group.

[3] A number of pre-1999 references relating to N-methylated amino acids are provided in the footnotes 1-3 to L. Aurelio et al, 2002 Organic Letters, 4(21):3767-3769, which establish knowledge in the art as of the priority filing date of this application.

Claim 140 further states that the peptide is a modified, non-naturally-occurring pyrrhocoricin-derived peptide that lacks the mid-chain glycosylation of the Thr residue of naturally-occurring pyrrhocoricin. This language is supported by the specification's (and the published art) description of naturally-occurring pyrrhocoricin which is glycosylated at the mid-chain and ***sole*** Thr residue and the specification's description of its deglycosylated pyrrhocoricin Peptide 1 at pages 5, lines 1-2 and 26-27, and 23, lines 26-30. The clear import of this disclosure indicates to one of skill in the art that the "deglycosylation" referenced is that at pyrrhocoricin's mid-chain Thr and thus the corresponding Thr in the modified pyrrhocoricin peptides. With respect, the amended claim language in claim 140 is supported by the clear meaning of the specification.

New claim 140 also contains the provision that the modified peptides have antibacterial activity, as supported at page 5, lines 1-8; page 13, lines 11-17 and in Example 4. Claim 140 is submitted to overcome all the section 112, first paragraph rejections, previously addressed against claim 1.

With regard to the examiner's rejections of the dependent claims requiring the attachment of additional peptides, the language of Claim 140 as to the function of antibacterial activity as well as the assays described therefore in Example 4 are sufficient for one of skill in the art to determine whether any composition falls under the scope of the dependent claims.

Because the term "dipeptide" is not used in Claim 140 and claim 73 now depends from claim 140, the rejection of Claim 73 may be properly withdrawn.

Applicants respectfully disagree with the examiner's position regarding the adequacy of the disclosure of the nature of the spacer sequence and additional amino acids in view of this functional feature of the independent claim. One of skill in the art may readily use the assays described in the specification as well as others known in the art to determine stability in serum and anti-bacterial nature of the claimed peptides and compositions.

The claim amendments set forth above are believed to satisfy all of the examiner's section 112 rejections.

Reconsideration of this rejection is requested.

35 USC § 112, Second Paragraph, Rejection

The Examiner rejected claims 1, 73-76, 79, and 82-139 under 35 USC § 112, second paragraph for allegedly being indefinite.

The Examiner asserted that the claims should properly read "R^1 *-SEQ ID NO: 1 –* R^2*" as discussed above with respect to the specification, that Markush language should be corrected, the term "unnatural amino acids" should be defined, the phrase "optionally substituted" should be corrected; and antecedent basis should be corrected in the claims. Additionally, claims 75, 76, 82, 84 are rejected for use of the terms "other peptides", "the second or additional or other", and "effective amount" etc.*

Applicant respectfully requests reconsideration and withdrawal of this rejection for the following reasons.

In view of the amendments made to the claims above, Applicant submits that all indefinite language has been eliminated from the pending claims.

Reconsideration of this rejection is requested.

35 USC § 102(b)/103(a) Rejection

The Examiner rejected claims 1, 111, 112 and 128 under 35 USC §102(b) or alternatively under 103(a), as being anticipated or made obvious over International patent publication No. WO94/05787 (Bulet), which allegedly teaches the claimed peptide with 100% sequence identity and non-glycoslyated peptides thereof, in which R^1 *is Val, X is Ser, Y is Tyr, X' is Asn, Y' is Arg. The examiner alleges that the Thr in the sequence is non-glycosylated, based on the teaching that the peptide itself is not glycosylated (page 1, line 32).*

Applicant respectfully requests reconsideration and withdrawal of this rejection for the following reasons. Bulet does not teach or suggest the modified pyrrhocoricin-based peptides encompassed by the present claims.

In the discussion of Bulet hereafter, Applicant refers to pages and line numbers of the English translation of Bulet kindly provided by the Examiner. Bulet refers to multiple insect glycopeptides that have antibacterial properties and discusses the effect of the presence of certain substitution groups in aminated acids, which provide at least some

of the substituted peptides with a high activity level[4]. Bulet notes that the substituted aminated acid is a hydroxylated aminated acid, e.g. Thr, Ser or Tyr.[5] One preferred modification of Bulet's peptides involves substitutions ***on the glycosyl group***.[6] Bulet explicitly states that

> " ..the glycosylic groups mentioned rather astonishingly appear ***indispensable*** in having an appreciable level of antibacterial activity." (emphasis added)[7]

Bulet discusses a variety of non-pyrrhocoricin sequences in which glycosyl group substitutions are made on a Ser or Thr in the respective sequences.

However, Bulet does not explicitly describe any peptide modification other than the glycosyl modifications discussed above. The only other teachings of Bulet regarding peptide modifications include a generic statement that other glycopeptides of the invention comprise more complex substitutions involving the terminal N and/or C parts and/or substitutions by radicals of sialic acid,[8] that fragments or variants are contemplated[9], that one or several aminated acids are deleted or substituted by a group other than a glycosyl or replaced by another aminated acid having a neighboring charge[10].

The examples describe, inter alia, the deglycosylation of a synthetic peptide (not a pyrrhocoricin-derived peptide) as reducing the biological activity.[11] In Example 5, using another peptide, Bulet states that O-glycosylation is ***necessary*** for the biological activity of the peptides.[12]

Bulet's SEQ ID NO: 9 is the same sequence as Applicant's R^1 -SEQ ID NO: 1-R^2, in which R^1 is Val, X and Y are Ser-Tyr and X' and Y' are Asn-Arg and R^2 is Asn,

---

4 Page 3, lines 23-24 to page 4, line 6 of the translation provided by the examiner.
5 Page 4, lines 15-22 of the translation.
6 Page 5, lines 3 et seq.; page 16 of the translation.
7 Page 6, lines 13-16; emphasis added.
8 Page 6, lines 10-12 of the translation.
9 Page 17, lines 10 et seq. of the translation.
10 Page 17, lines 17-20 of the translation.
11 Page 29, lines 16-18 of the translation.
12 Page 34, lines 10-12 of the translation.

and as stated explicitly by Bulet: "In this sequence the threonine charge is in position 11 and ***is substituted by a glycosyl group as defined above.***"[13]

Nowhere throughout this specification does Bulet provide any teachings of any specific modification of this pyrrhocoricin-based sequence. Nothing in Bulet's teachings of modification of other peptides suggests the modifications recited in the pending claims, since the pending claims do **not** encompass substitution of the glycosyl group of pyrrhocoricin, but the ***elimination*** thereof. Further, based on Bulet's teachings regarding the crucial nature of glycosylation in the other non-pyrrhocoricin based peptides in this disclosure, Bulet can be interpreted to ***teach away*** from non-glycosylated pyrrhocoricin-based peptides as providing biologically active peptides. Further, Bulet does not state anything with regard to increased stability to mammalian serum enzymes as a result of any modification.

Therefore, Bulet does not teach the pyrrhocoricin-based peptides encompassed by Applicant's claims and in fact teaches away from non-glycosylated pyrrhocoricin. Bulet does not suggest to the person of skill in the art the specific peptide modifications encompassed by Applicant's claims, nor the effect thereof in enhancing stability to enzymatic degradation nor enhancement of biological stability. Bulet may be withdrawn as a basis for either an anticipation or obviousness rejection of the pending claims.

Reconsideration of this rejection is respectfully requested.

Supplemental Information Disclosure Statement

Applicant further supplies with this response a supplemental Information Disclosure Statement providing the post-filing publications of the inventor as well as other documents cited herein and a copy of the Office Action in the corresponding European application.

---

[13] Page 17, lines 7-8 of the translation.

The Director is hereby authorized to charge any deficiency in any fees due with the filing of this paper or credit any overpayment in any fees to our Deposit Account Number 08-3040.

Respectfully submitted,

HOWSON AND HOWSON
Attorneys for Applicants

By _____
Mary E. Bak
Registration No. 31,215
Spring House Corporate Center
Box 457
Spring House, PA 19477
(215) 540-9200